65. (New) The method of claim 62 or 63, wherein said mutant retrovirus is a multidrug-resistant HIV retrovirus.

66. (New) The method of claim 62 or 63, wherein said mutant retrovirus is a multidrug-resistant HIV-1 retrovirus.

REMARKS

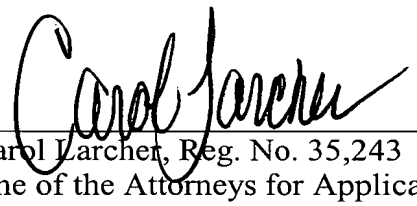
Claims 11-15, 18, 19, 30-34, 37, 38, 43, 49-51 and 54-62 have been amended to remove the multiple dependencies so that each claim is dependent on a single claim. Claims 24 and 28 have been amended to correct obvious typographical errors. Claim 47 has been amended to more particularly define the structure of substituent A. In addition, the text "or R^5 and R^6 together with the N-W bond of formula (I) comprise a 12 to 18 membered ring..." was deleted from claim 47. Claim 47 has also been amended to further define substituent R^4 to include esters, amides and other amine derivatives, support for which can be found in the specification at, for example, page 35, lines 15-20. Claim 47 also has been amended with respect to the definitions of substituents Y and Z, and substituents R^{12}, R^{13} and R^{15-17}, by reciting the transitional phrase "are the same or different and each is." This amendment is a matter of form only and is supported by the claim as originally filed. New claims 63-66 have been added. Support for the new claims can be found in the specification at, for example, page 57, line 10, to page 58, line 17, page 60, line 10, to page 61, line 9, and page 76, line 1, to page 83, line 3. Claim 48 has been cancelled.

The foregoing amendments and new claims are fully supported by the specification. Thus, no new matter has been added.

Separate documents setting forth the precise changes to the claims, as well as the text of all the pending claims, are enclosed herewith.

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: December 21, 2000

In re Appln. of Erickson et al.
U.S. National Phase of PCT/US99/14119

CERTIFICATE OF MAILING

I hereby certify that this PRELIMINARY AMENDMENT (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: 12/21/00 Elizabeth M. Cogbill

AMDREG (Rev. 6/20/2000)

PATENT
Attorney Docket No. 207596

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Erickson et al.

Art Unit: Unassigned

U.S. National Phase of
PCT/US99/14119

Examiner: Unassigned

International Filing Date:
June 23, 1999

For: FITNESS ASSAY AND
ASSOCIATED METHODS

Mark-up Amd. Copy

AMENDMENTS TO CLAIMS ON DECEMBER 21, 2000

11. The assay of [any one of claims 1-10] claim 1, wherein said biochemical target of said predecessor is an enzyme and said compound inhibits said enzyme of said predecessor.

12. The assay of [any one of claims 3-5] claim 1, wherein said biochemical target of said predecessor is a viral protease, a viral reverse transcriptase, a viral polymerase, a viral enzyme, or a viral protein.

13. The assay of claim [6 or 7] 1, wherein said biochemical target of said malarial parasite is a plasmepsin, a plasmodial enzyme, or a protein.

14. The assay of [any one of claims 1-10] claim 1, wherein said biochemical target of said predecessor is an oligomer and said compound inhibits the oligomerization of said oligomer of said predecessor.

15. The assay of [any one of claims 1-10] claim 1, wherein said biochemical target of said predecessor is a protein and said compound inhibits a conformational change, ligand binding, or enzyme activity in said protein of said predecessor.

18. The assay of claim 16 [or 17], wherein K_{inh} is K_i.

19. The assay of claim 16 [or 17], wherein K_{inh} is K_d.

24. The method of claim 23, wherein said retrovirus is [HIV] HIV-1 or HIV-2.

28. The method of claim 20, wherein said [replicating] disease-causing replicating biological entity is a cancer cell.

30. The method of [any one of claims 20-29] claim 20, wherein said biochemical target of said disease-causing replicating biological entity is an enzyme and said compound inhibits said enzyme of said disease-causing replicating biological entity.

31. The method of [any one of claims 22-24] claim 22, wherein said biochemical target of said disease-causing replicating biological entity is a viral protease, a viral reverse transcriptase, a viral polymerase, a viral enzyme, or a viral protein.

32. The method of claim 25 [or 26], wherein said biochemical target of said malarial parasite is a plasmepsin, a plasmodial enzyme, or a protein.

33. The method of [any one of claims 20-29] claim 20, wherein said biochemical target of said disease-causing replicating biological entity is an oligomer and said compound inhibits the oligomerization of said oligomer of said disease-causing replicating biological entity.

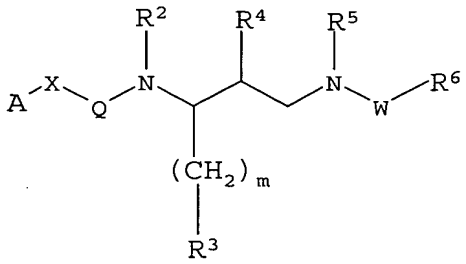
34. The method of [any one of claims 20-29] claim 20, wherein said biochemical target of said disease-causing replicating biological entity is a protein and said compound inhibits a conformational change, ligand binding, or enzyme activity in said protein of said disease-causing replicating biological entity.

37. The method of claim 35 [or 36], wherein K_{inh} is K_i.

38. The method of claim 35 [or 36], wherein K_{inh} is K_d.

43. The method of claim 39 [or 40], wherein said mutant has at least one active site mutation.

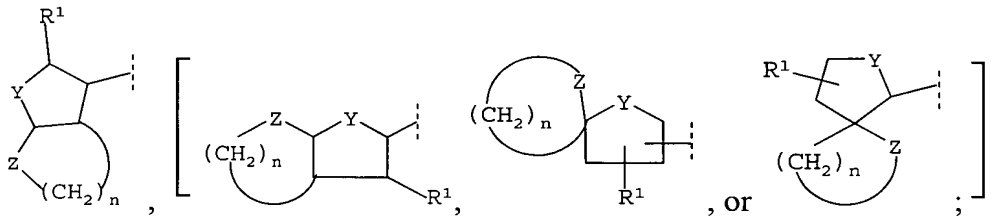
47. A method of preventing the development of drug resistance in an HIV-infected mammal, said method comprising administering to said HIV-infected mammal a drug resistance-inhibiting effective amount of a compound of the formula:



(I),

or a pharmaceutically acceptable salt, a prodrug, or an ester thereof, or a pharmaceutically acceptable composition of said compound, said salt, said prodrug, or said ester thereof, wherein:

A is a group of the formula:



R^1 is H or an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkylalkyl, an aryl, an aralkyl, a heterocycloalkyl, a heterocycloalkylalkyl, a heteroaryl, or a heteroaralkyl, in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of OR^7, SR^7, CN, NO_2, N_3, and a halogen, wherein R^7 is H, an unsubstituted alkyl, an unsubstituted alkenyl, or an unsubstituted alkynyl;

Y and Z are the same or different and [are independently] <u>each is</u> selected from the group consisting of CH_2, O, S, SO, SO_2, NR^8, $R^8C(O)N$, $R^8C(S)N$, $R^8OC(O)N$, $R^8OC(S)N$, $R^8SC(O)N$, $R^8R^9NC(O)N$, and $R^8R^9NC(S)N$, wherein R^8 and R^9 are each selected from the group consisting of H, an unsubstituted alkyl, an unsubstituted alkenyl, and an unsubstituted alkynyl;

n is an integer from 1 to 5;

X is a covalent bond, CHR^{10}, $CHR^{10}CH_2$, CH_2CHR^{10}, O, NR^{10}, or S, wherein R^{10} is H, an unsubstituted alkyl, an unsubstituted alkenyl, or an unsubstituted alkynyl;

Q is C(O), C(S), or SO_2;

R^2 is H, a C_1-C_6 alkyl, a C_2-C_6 alkenyl, or a C_2-C_6 alkynyl;

m is an integer from 0 to 6;

R^3 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of alkyl, $(CH_2)_pR^{11}$, OR^{12}, SR^{12}, CN, N_3, NO_2, $NR^{12}R^{13}$, $C(O)R^{12}$, $C(S)R^{12}$, CO_2R^{12}, $C(O)SR^{12}$, $C(O)NR^{12}R^{13}$, $C(S)NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}C(S)R^{13}$, $NR^{12}CO_2R^{13}$, $NR^{12}C(O)SR^{13}$, and a halogen, wherein:

p is an integer from 0 to 5;

R^{11} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OH, OCH_3, NH_2, NO_2, SH, and CN; and

R^{12} and R^{13} are [independently] <u>the same or different and each is</u> selected from the group consisting of H, an unsubstituted alkyl, an unsubstituted alkenyl, and an unsubstituted alkynyl;

R^4 is OH, =O (keto)[, NH_2, or $NHCH_3$] <u>or NH_2, wherein, when R^4 is OH, it is optionally in the form of a pharmaceutically acceptable ester or prodrug, and when R^4 is NH_2, it is optionally an amide, a hydroxylamino, a carbamate, a urea, an alkylamino, a dialkylamino, a protic salt thereof, or a tetraalkylammonium salt thereof;</u>

R^5 is H, a C_1-C_6 alkyl radical, a C_2-C_6 alkenyl radical, or $(CH_2)_qR^{14}$, wherein q is an integer form 0 to 5, and R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl

radical in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OH, OCH_3, NH_2, NO_2, SH, and CN;

W is C(O), C(S), or SO_2; and

R^6 is a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN, $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3, NO_2, $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, $P(O)(OR^{15})(OR^{16})$, an alkyl, an alkoxy, an alkylthio, an alkylamino, a cycloalkyl, a cycloalkylalkyl, a heterocycloalkyl, a heterocycloalkylalkyl, an aryl, an aryloxy, an arylamino, an arylthio, an aralkyl, an aryloxyalkyl, an arylaminoalkyl, an aralkoxy, an (aryloxy)alkoxy, an (arylamino)alkoxy, an (arylthio)alkoxy, an aralkylamino, an (aryloxy)alkylamino, an (arylamino)alkylamino, an (arylthio)alkylamino, an aralkylthio, an (aryloxy)alkylthio, an (arylamino)alkylthio, an (arylthio)alkylthio, a heteroaryl, a heteroaryloxy, a heteroarylamino, a heteroarylthio, a heteroaralkyl, a heteroaralkoxy, a heteroaralkylamino, and a heteroaralkylthio,

wherein R^{15}, R^{16}, and R^{17} are the same or different and each is H, an unsubstituted alkyl, or an unsubstituted alkenyl,

wherein, when at least one hydrogen atom of R^6 is substituted with a substituent other than a halogen, OR^{15}, SR^{15}, CN, N_3, NO_2, $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$,

$NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$, at least one hydrogen atom on said substituent is optionally substituted with a halogen, OR^{15}, SR^{15}, CN, N_3, NO_2, $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$; [or

R^5 and R^6 together with the N-W bond of formula (I) comprise a 12 to 18 membered ring, comprising at least one additional heteroatom in the ring skeleton other than the nitrogen of said N-W bond;] and

wherein a mutant virus that is capable of evolving from the HIV virus infecting said mammal has lower fitness, relative to said HIV virus infecting said mammal, in the presence of said compound.

49. The method of claim 47 [or 48], wherein:

when R^1 is an alkyl, it is a C_1-C_6 alkyl;

when R^1 is an alkenyl it is a C_2-C_6 alkenyl;

when R^1 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, R^1 is a 4-7 membered ring;

when R^7, R^8 or R^9 is an unsubstituted alkyl, it is a C_1-C_6 unsubstituted alkyl;

when R^7, R^8 or R^9 is an unsubstituted alkenyl, it is a C_2-C_6 unsubstituted alkenyl;

R^3 is a 4-7 membered ring;

R^{11} is a 4-7 membered ring;

when R^{12} or R^{13} is an unsubstituted alkyl, it is a C_1-C_6 unsubstituted alkyl;

when R^{12} or R^{13} is an unsubstituted alkenyl, it is a C_2-C_6 unsubstituted alkyl;

when R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, R^{14} is a 4-7 membered ring;

when R^6 is a cycloalkyl, a heterocycloalkyl, aryl, or a heteroaryl, R^6 is a 4-7 membered ring;

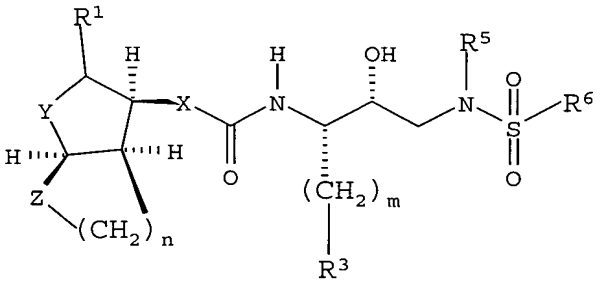
when R^6 is substituted with a substituent that is an alkyl, an alkylthio, or an alkylamino, the substituent comprises from one to six carbon atoms; and

when R^6 is substituted with a substituent that is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, the substituent is a 4-7 membered ring;

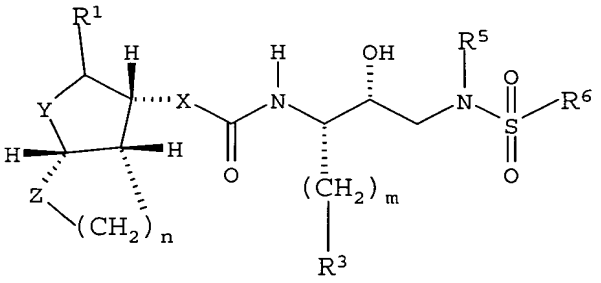
or a pharmaceutically acceptable salt, a prodrug, or an ester thereof.

50. The method of [any one of claims 47-49] claim 47, wherein Q is C(O), R^2 is H, and W is SO_2, or a pharmaceutically acceptable salt, a prodrug, or an ester thereof.

51. The method of claim [48] 47, wherein said compound is represented by the formula:



(IA) or



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54. The method of claim 52 [or 53], wherein X is oxygen.

55. The method of claim 52 [or 53], wherein R^5 is isobutyl.

56. The method of claim 52 [or 53], wherein Ar is a phenyl substituted at the para-position.

57. The method of claim 52 [or 53], wherein Ar is a phenyl substituted at the meta-position.

58. The method of claim 52 [or 53], wherein Ar is a phenyl substituted at the ortho-position.

59. The method of claim 52 [or 53], wherein Ar is selected from the group consisting of para-aminophenyl, para-toluyl, para-methoxyphenyl, meta-methoxyphenyl, and meta-hydroxymethylphenyl.

60. The method of [any one of claims 47, 48, or 51-53] claim 47, wherein said HIV-infected mammal is infected with a wild-type HIV.

61. The method of [any one of claims 47, 48, or 51-53] claim 47, wherein said HIV-infected mammal is infected by a mutant HIV with least one protease mutation.

62. The method of [any one of claims 47, 48, or 51-53] claim 47, wherein said HIV-infected mammal is infected by a mutant HIV having at least one reverse transcriptase mutation.

63. (New) A method of treating a mutant retroviral infection in a mammal infected with a mutant retrovirus, which method comprises administering to said mammal a mutant retroviral-inhibiting effective amount of a compound or composition defined in claim 47.

64. (New) The method of claim 62 or 63, wherein said mutant retrovirus is a multidrug-resistant mutant retrovirus.

65. (New) The method of claim 62 or 63, wherein said mutant retrovirus is a multidrug-resistant HIV retrovirus.

66. (New) The method of claim 62 or 63, wherein said mutant retrovirus is a multidrug-resistant HIV-1 retrovirus.